CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA 125487/0
Product: antihemophilic factor [recombinant Fc fusion protein]
Sponsor: Biogen Idec
Indication: For the treatment of hemophilia A indicated in adults and children (≥ 2 years)
Date Received: March 08, 2013
Reviewer: Carl-Michael Staschen, M.D., Ph.D.
RPM: Leigh Pracht
Through: Iftekhar Mahmood Ph.D. and Basil Golding, M.D.

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Study #1: A Phase I/IIa, open-label, crossover, dose-escalation, and multi-center study to determine the safety, tolerability, and pharmacokinetics of a single intravenous injection of rFVIIIFc in previously treated patients with severe hemophilia A (Study No. 997HA301).

Study #2: An open-label, multi-center evaluation of the safety, pharmacokinetics, and efficacy of recombinant, factor VIII Fc fusion protein (rFVIIIFc) in the prevention and treatment of bleeding in previously treated subjects with severe hemophilia A. (Study Number: 998HB102)

Study #3: Pharmacometric study report. (Report No. CPP-12-026-BIIB031).

Study #4 (Interim Report): An open-label, multicenter evaluation of safety, pharmacokinetics, and efficacy of recombinant coagulation factor VIII Fc fusion protein, in the prevention and treatment of bleeding episodes in pediatric subjects with hemophilia A. (Study Number: 8HA02PED)

EXECUTIVE SUMMARY

Background:

Hemophilia A is an X-chromosome-linked coagulation disorder that primarily affects males. It is caused by mutations and/or deletions in the FVIII gene, resulting in a deficiency of FVIII activity. The severity of disease is characterized by the endogenous level of FVIII activity measured in the plasma. Severe hemophilia A is defined as a coagulation activity of FVIII achieving only plasma concentrations of <1%. Individuals with severe hemophilia A experience frequent bleeding and recurrent spontaneous bleeding into the soft tissue and joints, leading to joint damage and severe disability with major effects on physical and psychosocial parameters, quality of life (QoL), and financial burden.

There is no currently available cure for hemophilia A. Current treatment focuses on factor replacement therapy with plasma-derived (pdFVIII) or recombinant FVIII (rFVIII) products. A limitation of FVIII therapy is a short half-life (~12 hours) necessitating frequent infusions.

Biogen Idec's recombinant drug product fusion protein rFVIIIFc consists of a single molecule of human coagulation FVIII covalently attached to the dimeric Fc domain of human IgG1. The rFVIIIFc drug substance is produced in human embryonic kidney 293 (HEK-293) cell line. The Fc portion enables binding to the neonatal Fc receptor (FcRn), which is responsible for protecting IgG from degradation. The FcRn is present in humans throughout life and protects IgG from catabolism. rFVIIIFc is designed to offer a longer circulating half-life than currently available FVIII products, aiming to provide hemophilia A patients with prolonged protection and prophylaxis from bleeding with less frequent dosing.

Proposed Indication

Biogen Idec is seeking approval for rFVIIIFc for the following indication:

- Control and prevention of bleeding episodes.
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Perioperative management (surgical prophylaxis)

The following is the summary of the 4 submitted PK studies.

PK concentration-profile in all studies were determined based on the disposition of plasma FVIII activity over time as measured by a validated one-stage aPTT clotting assay and by a –b(4)---chromogenic substrate assay. The PK data analyses were performed using either compartmental or noncompartmental analyses.

A Phase 1/2a study investigated rFVIIIFc in 16 male (≥ 12 yr) previously treated subjects with severe hemophilia A (defined as <1% endogenous factor VIII). The study was designed as an open-label, multicenter, dose-escalation study to evaluate the safety and PK of a single dose of

rFVIIIFc (-b(4)-------- formulation) given as an IV injection over approximately 10 minutes. Six (6) subjects at the low dose level and 10 subjects at the high dose level were enrolled in this study. The study compared a single dose of rFVIIIFc at doses of 25 IU/kg and 65 IU/kg, with a single dose of the competitor Advate® at the same dose levels (IU/kg). For the one-stage aPTT assay the estimated mean clearances of rFVIIIFc were 1.72 mL/kg/h [95%-CI: 1.3, 2.2] at 25 IU/kg and 2.55 mL/kg/h [95%-CI: 1.6, 3.5] at 65 IU/kg. The mean elimination half-lives were 19.2 h [95%-CI: 15, 24] at 25 IU/kg and 19.8 h [95%-CI: 15, 25] at 65 IU/kg. For Advate® the estimated mean elimination half-lives (h) were 10.7 (25 IU/kg) and 11.4 (65 IU/kg). PK parameters derived from the –b(4)----- chromogenic assay data were generally consistent with those generated from the one-stage aPTT assay data. No inhibitors or anti-rFVIIIFc antibodies were detected during the study.

The Phase 3 study was an open-label, multicenter study to evaluate the safety, PK, and efficacy of rFVIIIFc (lyophilized powder) administered as an IV injection to PTP (≥ 12 y) with severe hemophilia A (defined as <1% endogenous factor VIII). A total of 155 subjects had PK assessments and periodic trough/peak measurements were done during the study. The study evaluated an individualized prophylaxis regimen (Arm 1), a weekly prophylaxis regimen (Arm 2), and an episodic (on-demand) regimen (Arm 3). A subgroup of subjects from any arm requiring major surgery during the study was also evaluated. The PK subgroup in Arm 1 (N = 29) received sequential single IV doses of 50 IU/kg Advate® (competitor) and rFVIIIFc for direct comparison of detailed PK profiles.
After a dose of 50 IU/kg the mean incremental recovery (IR) (IU/dL per IU/kg) of rFVIIIFc was 2.26 [95%-CI: 2.1, 2.4], the mean clearance was estimated to be 2.06 mL/h/kg [95%-CI: 1.8, 2.3], and the mean elimination half-life (T½) was 17.8 hours [95%-CI: 17, 19]. Overall, the PK profiles and estimated PK parameters of adolescents (N = 11) were similar to adults (N = 144). Compared to the competitor Advate®, rFVIIIFc showed a 1.53-fold (53%) longer elimination half-life. PK parameters derived from the –b(4)------ chromogenic assay data were generally consistent with those generated from the one-stage aPTT assay data.
No subject had a confirmed positive inhibitor test result. There were 11 subjects with anti-rFVIIIFc binding antibody positive test results. No impact of a positive anti-rFVIIIFc binding antibody test result on PK was detected.

A nonlinear mixed effects (population) PK analysis was performed by combining PK data from the clinical Phase 1/2a and Phase 3 studies to describe the disposition of rFVIIIFc. Overall, the estimated population PK parameters of rFVIIIFc were derived from a 2-compartment PK model. The following key points summarize the analysis:

- The final 2-compartment population PK model for rFVIIIFc describes adequately the combined activity data from the Phase 1/2a and Phase 3 studies. The major identified covariate was the von Willebrand Factor level on clearance.

- The results of the population PK analyses for rFVIIIFc and Advate® confirm that the systemic clearance of rFVIIIFc is lower than the clearance of Advate®, while the volumes of distribution at steady state are very similar.

The ongoing pediatric study (8HA02PED) is an open-label, multicenter evaluation of the safety, PK, and efficacy of rFVIIIFc for routine prophylaxis and control of bleeding in previously treated patients <12 years of age with severe hemophilia A (defined as <1% endogenous factor VIII). Thirty-seven (37) pediatric subjects (10 subjects 2 to <6 years of age and 27 subjects 6 to <12 years of age) had evaluable rFVIIIFc PK profiles. At this point in time the following conclusions can be drawn from this study:

- Compared to adults, there is a substantial relative increase in mean bodyweight adjusted CL = +58% in pediatric patients 2 to < 6 years of age. These differences should be taken into account when dosing children 2 to < 6 years of age. Only minor differences were noted between adults and children 6 to < 12 yr.
- An average half-life of 12 h was estimated in pediatric patients 2 to < 6 years of age. In a different study the mean half-life in adults was determent to be 18 h.
- PK parameters derived from the two-stage chromogenic assay data were generally consistent with those generated from the one-stage aPTT assay data.

OVERALL COMMENTS

- In general, the PK results and conclusions of the Phase 1/2a, Phase 3, and ongoing pediatric PK study are acceptable from a Clinical Pharmacology perspective.
- The results of the pharmacometric study report for rFVIIIFc show severe deficiencies and are not acceptable. Based on the estimated population parameters of the final 2-compartment model, the post-hoc calculated terminal half-life of rFVIIIFc is around 68 h. This is inconsistent with the estimated half-life determined in the Phase 1/2a study (≈ 19 h) and in the Phase 3 study (≈ 17 h). However, this analysis deficiency will not be considered for clinical pharmacology labeling of rFVIIIFc.
- To evaluate adequate dosing regimens for routine prophylaxis stochastic simulations (5000 virtual adult patients) covering two dose levels (50 IU/kg and 65 IU/kg) were carried out by this reviewer. These simulations were based on PK results of the Phase 1/2a study.

  The simulations for prophylactic treatment predicted that at a dose of 65 IU/kg of rFVIIIFc every 5 days 84% of the patient population had FVIII $C_{(trough)}$ concentrations > 1 IU/dL (1%). However, simulations of 65 IU/kg of rFVIIIFc every 7 days predicted only 24% of the patient population with $C_{(trough)}$ > 1 IU/dL. Simulations at a dose of 50 IU/kg of rFVIIIFc every 5 days revealed that 76% of the patient population had FVIII $C_{(trough)}$

concentrations > 1 IU/dL. Based on these results, the applicant's proposed dosing regimen of 65 IU/kg every 7 days is not acceptable. To achieve and sustain therapeutic concentrations in the majority of patients a dose of either 65 IU/kg or 50 IU/kg with a dosing frequency of every 5 days appears to be sufficient.

- To assess adequate dosing regimens for routine prophylaxis in pediatric hemophilia A patients (2 to 6 yr) stochastic simulations covering a dose of 80 IU/kg were carried out by this reviewer. These simulations were based on preliminary PK results of the ongoing pediatric Phase 3 study.

  The simulations for prophylactic treatment in children using 80 IU/kg of rFVIIIFc administered every 5, 4, and 3 days indicated that 40%, 65%, and 90%, patient population will have FVIII $C_{(trough)}$ concentrations > 1 IU/dL (1%), respectively, To achieve and sustain therapeutic concentrations in the majority of this pediatric subgroup a dose of 80 IU/kg with a dosing frequency of every 3 days appears to be sufficient.
- A final assessment of the pediatric PK study can only be made after submission of the final study report.

CLINICAL PHARMACOLOGY LABELING COMMENTS

Page 1: Use In Specific Population.

Pediatric: Safety, efficacy, and pharmacokinetics of ELOCTATE have been evaluated in previously treated pediatric patients ages 2 to 12 years and older. No dose adjustment is required for patients > 6 years. In pediatric patients ~~less than 12~~ 2 to 6 years of age, clearance based on per kg basis increased and in line with this result half-life ~~may be~~ decreased, ~~potentially~~ requiring dose adjustment. (8.4)

8.4 Pediatric Use

Safety, efficacy, and pharmacokinetics of ELOCTATE have been evaluated in previously treated pediatric patients 2 to 12 years of age and older. No dose adjustment is required for patients > 6 years. In comparison with children (> 6 years), adolescents, and adults, children ~~less than 12~~ 2 to 6 years of age ~~may~~ have a shorter half-life. The body weight adjusted clearance is 58% higher in children 2 to 6 years of age (3.88 vs. 2.46 mL/hr/kg) compared to adults. This difference should be taken into account when dosing. A higher dose or more frequent dosing may be needed in patients ~~less than 12~~ 2 to 6 years of age. [*see Pharmacokinetics (12.3)*]

Section 12.3 Pharmacokinetics

Comment: the complete subsection "Pharmacokinetic Properties" should be deleted and replaced because labeling information should only focus on the sponsor's submitted drug product and not on the drug of the competitor.

~~**Pharmacokinetic Properties**~~

~~The pharmacokinetics (PK) of ELOCTATE (rFVIIIFc) versus Advate® (rFVIII) was evaluated following a 10-minute IV infusion in 28 evaluable subjects (≥ 15 years). Subjects underwent a washout period of at least 4 days prior to receiving a single 50 IU/kg dose of Advate. PK sampling was conducted pre-dose and then subsequently at 6 time points up to 72 hours post-dose. Following a washout period of at least 96 hours (4 days), subjects received a single dose of 50 IU/kg of ELOCTATE. PK samples were collected pre-dose and then subsequently at 7 time points up to 120 hours (5 days) post-dose. A repeat PK evaluation of ELOCTATE was conducted at Week 14.~~

~~PK parameters for ELOCTATE were estimated based on the plasma FVIII activity over the time profile. For ELOCTATE, the maximum activity (C_{max}) was observed following the end of the infusion. The geometric mean increase in circulating FVIII activity from pre-infusion level was 2.24 IU/dL per IU/kg and the elimination half-life was 19 hours. This half-life is influenced by the Fc region of ELOCTATE, which in animal models was shown to be mediated by the FcRn cycling pathway. The ELOCTATE PK profile was stable over repeated dosing as shown by comparable PK parameters at Week 14.~~

~~A summary of PK parameters after a 50 IU/kg dose for ELOCTATE and Advate are presented in Table 1. The mean observed activity time profile for ELOCTATE and Advate is presented in Figure 1.~~

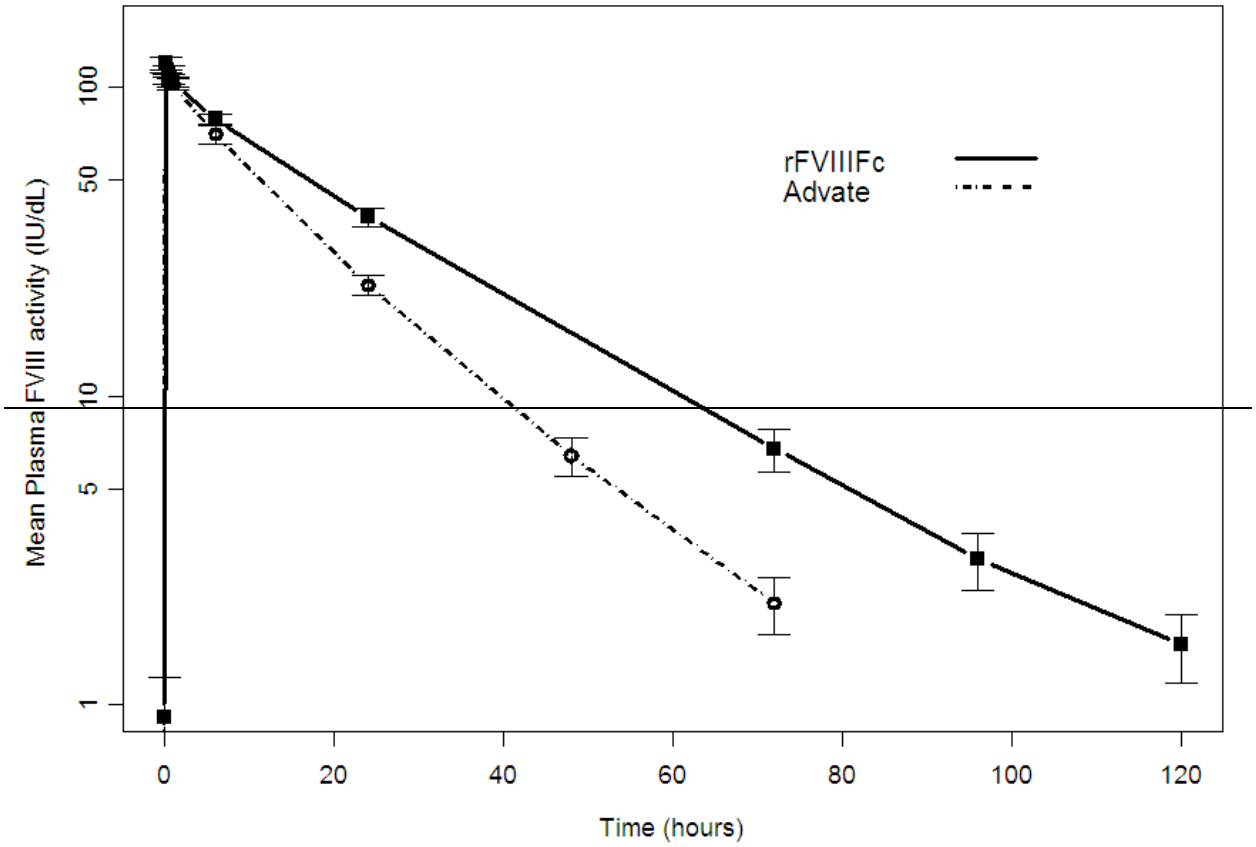
Table 1: Pharmacokinetic Parameters of ELOCTATE (rFVIIIFc) and Advate (rFVIII) (single 50 IU/kg dose)

PK Parameters[1]	ELOCTATE (95% CI)	Advate (95% CI)	Ratio of ELOCTATE to Advate (95% CI)
-	N=28	N=28	N=28
C_{max} (IU/dL)	108 (101, 115)	120 (111, 128)	0.90 (0.86, 0.95)
AUC/Dose (IU*h/dL per IU/kg)	51.2 (45.0, 58.4)	32.9 (29.3, 36.9)	1.56 (1.46, 1.67)
Terminal half-life (h)	19.0 (17.0, 21.1)	12.4 (11.1, 13.9)	1.53 (1.36, 1.71)
CL (mL/h/kg)	1. 95 (1.71, 2.22)	3.04 (2.71, 3.41)	0.64 (0.60, 0.69)
MRT (h)	25.2 (22.7, 27.9)	16.8 (15.2, 18.6)	1.49 (1.41, 1.58)
V_{ss} (mL/kg)	49.1 (46.6, 51.7)	51.2 (47.2, 55.5)	0.96 (0.90, 1.02)
Incremental Recovery (IU/dL per IU/kg)	2.24 (2.11, 2.38)	2.35 (2.21, 2.50)	0.95 (0.91, 0.99)
Time to 1% (days)	4.918 (4.434, 5.455)	3.298 (2.985, 3.645)	1.49 (1.41, 1.57)

[1]PK parameters are presented in Geometric Mean (95% CI)

Abbreviations: CI = confidence interval; C_{max} = maximum activity; AUC = area under the FVIII activity time curve; CL = clearance; MRT = mean residence time; V_{ss} = volume of distribution at steady-state

~~**Figure 1: Mean (+/- SE*) Observed Activity Profile for ELOCTATE (rFVIIIFc) and Advate (rFVIII)**~~



~~*SE: standard error~~

Pharmacokinetics: ~~Properties~~

In a Phase 1/2a study, 15 previously treated male subjects with severe hemophilia A received a single dose of 25 IU/kg and 65 IU/kg of ELOCTATE given as an IV injection. The estimated PK parameters were based on plasma FVIII activity measured by one-stage activated partial thromboplastin time (aPTT) clotting assay. Observed Cmax values appear to be dose proportional 65.9 IU/dL (25 IU/kg) and 120 IU/dL (65 IU/kg). The estimated terminal half-lives were similar between the two doses 19.2 h (25 IU/kg) and 19.8 h (65 IU/kg). Relevant PK parameters are compiled in Table 5.

In a Phase 3 study, a PK subgroup of 28 subjects with severe hemophilia A received a single intravenous dose of 50 IU/kg ELOCTATE. The estimated PK parameters were based on plasma FIX activity measured by a one-stage activated partial thromboplastin time (aPTT) clotting assay. Relevant PK parameters are presented in Table 5. The estimated terminal half-life of 19.7 h was consistent with the results of the Phase 1/2a study. The observed Cmax value was 109 IU/kg and

IR (K-value) was calculated as 2.26 IU/dL per IU/kg. During repeated dosing the ELOCTATE PK profile was comparable at Week 14 with the PK profile obtained after the first dose.

In Table 5:

Please delete "Time to 3% (days)" because they do not add clinically relevant information.

Table 5: Pharmacokinetic Parameters (arithmetic Mean, 95%-CI) for rFVIIIFc activity data.

PK Parameter	998HA101 (Phase 1/2a)		997HA301 (Phase 3)
	rFVIIIFc 25 IU/kg Arithmetic Mean (N = 6) [95% CI]	rFVIIIFc: 65 IU/kg Arithmetic Mean (N = 9) [95% CI]	rFVIIIFc: 50 IU/kg Arithmetic Mean (N = 28) [95% CI]
C_{max_OB} (IU/dL)	60.9 [52.9,68.9]	120 [104 ,137]	109 [102, 116]
$t_{½}$ (h)	19.2 [14.7 ,23.6]	19.8 [14.8 ,24.7]	19.7 [17.4, 22.0]
MRT (h)	27.6 [21.1 ,34.0]	28.4 [21.3 ,35.6]	26.1 [23.2, 28.9]
CL (mL/h/kg)	1.72 [1.28 ,2.15]	2.55 [1.60 ,3.50]	2.06 [1.78, 2.34]
V (mL/kg)	45.8 [39.2 ,52.5]	63.6 [55.1 ,72.1]	49.5 [46.9, 52.2]
K-value (IU/dL per IU/kg)	2.46 [2.12 ,2.81]	1.85 [1.60 ,2.11]	2.26 [2.13, 2.40]
Time 1% (days)	4.52 [3.53 ,5.52]	5.46 [4.02 ,6.91]	5.10 [4.54, 5.66]
Time 3% (days)	3.30 [2.55 ,4.05]	4.15 [3.03 ,5.27]	3.85 [3.41, 4.29]

CI = confidence interval; CL = clearance; C_{max_OB} = maximum observed activity, occurring at T_{max} (baseline and residual drug subtracted); K-value = incremental recovery; MRT = mean residence time; PK = pharmacokinetic; $t_{½}$ = half-life; Time 1% = time after dose when FVIII activity has declined to 1 IU/dL above baseline; Time 3% = time after dose when FVIII activity has declined to 3 IU/dL above baseline.

Pediatric and Adolescent Pharmacokinetics:

Pharmacokinetic (PK) parameters of ELOCTATE (rFVIIIFc) were determined for adolescents (12 < 18 years) in the phase 3 study and for children (2 to < 6 years and > 6-12 years) in an open-label, multi-center study of pediatric previously treated patients. [*see Pediatric Use (8.4)*]

PK parameters were evaluated following a10-minute IV infusion in 11 adolescents and 37 children who received a single dose of ELOCTATE. PK parameters for ELOCTATE were estimated based on the plasma FVIII activity.

~~PK parameters were evaluated following a10-minute IV infusion in 11 evaluable adolescents who received a single dose of ELOCTATE. PK samples were collected pre-dose and then at multiple time points up to 120 hours (5 days) post-dose. In a separate study, PK parameters were evaluated following a 10-minute IV infusion in 37 evaluable children (2 to < less than 12 years of age) who received a single dose of ELOCTATE. PK samples were collected pre-dose and then at multiple time points up to 72 hours (3 days) post-dose. PK parameters for ELOCTATE were estimated based on the plasma FVIII activity over time profile~~

~~Table 6 presents the PK parameters calculated from the pediatric data of 48 subjects 2 to < less than 18 years of age.~~

Table **6** summarizes the PK parameters in adolescents and children. Compared to adults and adolescents, bodyweight-adjusted clearance ~~half-life~~ ~~appeared to be~~ is higher ~~shorter~~ in children ~~less than~~ 2 to 6 ~~12~~ years of age. This ~~may~~ results in a need for dose adjustments in children ~~less than~~ 2 to 6 ~~12~~ years of age. [*see Pediatric Use (8.4)*]

Comment: Table 6 parameter values need to be re-calculated based on arithmetic means.
Please add a row in Table 6 for the dose administered in each age group

Table 6: Comparison of PK Parameters of ELOCTATE (rFVIIIFc) by Age

PK Parameters[1]	Pediatric Study		Phase 3 Study
	2 to <6 Years (2, 5)	6 to <12 Years (6, 11)	12 to < 18 Years (12, 17)
	N = 10	N = 27	N = 11
IR (IU/dL per IU/kg)	~~1.878 (1.748, 2.017)~~	~~2.287 (2.004, 2.610)~~	~~1.807 (1.561, 2.092)~~
AUC/Dose (IU*h/dL per IU/kg)	~~27.06 (21.49, 34.07)~~	~~39.93 (33.94, 46.97)~~	~~38.15 (33.96, 42.87)~~
$t_{½}$ (h)	~~11.54 (9.41, 14.15)~~	~~13.22 (11.13, 15.71)~~	~~16.04 (13.90, 18.53)~~
MRT (h)	~~15.81 (12.94, 19.31)~~	~~19.22 (16.23, 22.77)~~	~~22.67 (19.67, 26.13)~~
CL (mL/h/kg)	~~3.697 (2.936, 4.654)~~	~~2.504 (2.128, 2.945)~~	~~2.621 (2.333, 2.945)~~
V_{ss} (mL/kg)	~~58.4 (54.7, 62.4)~~	~~48.1 (43.2, 53.7)~~	~~59.4 (52.7, 67.0)~~

[1]PK parameters are presented in Geometric Mean (95% CI)

Abbreviations: IR=incremental recovery; CI = confidence interval; AUC = area under the FVIII activity time curve; $t_{1/2}$ = elimination half-life; CL = clearance; MRT = mean residence time; Vss = volume of distribution at steady-state

The PK evaluation of the adolescent subjects 12 to < 18 years old showed that their PK profiles and the arithmetic means of PK parameters are similar to those of adults. Therefore, for subjects 12 years and older, an age-based dose adjustment is not required.

Comment: the subsection "Population Pharmacokinetics" should be completely deleted, because it does not add clinically relevant information for the prescribing and treating physician.

Population Pharmacokinetic Properties

A population PK model was developed based on PK data from 180 subjects, from 12 to 65 years old and weighing between 41 kg and 127.4 kg, in two clinical studies (16 subjects in a phase 1/2a study and 164 subjects in a phase 3 study). The population estimate for the typical CL of ELOCTATE is 1.65 dL/h, and V_{ss} is 44.4 dL. The model was used to predict the activity time profile following a single dose of ELOCTATE in patients with severe Hemophilia A [see Table 3]. In addition the model was used to predict trough activity for three different prophylaxis regimens [see Table 4].

Table 3: Predicted FVIII Activity [IU/dL] Following a Single Dose of ELOCTATE[1]

Dose (IU/kg)	Time (h)						
	EOI[2]	12	24	36	48	72	96
	Median (5th, 95th Prediction Interval)						
20	38.7 (27.3, 54.5)	22.7 (13.5, 35.0)	13.4 (5.79, 23.8)	7.92 (2.44, 16.7)	4.72 (1.06, 12.0)	1.79 (<0.5*, 6.52)	0.763 (<0.5*, 3.63)
25	48.4 (34.2, 68.1)	28.3 (16.9, 43.7)	16.8 (7.24, 29.8)	9.90 (3.05, 20.8)	5.90 (1.32, 15.0)	2.24 (<0.5*, 8.15)	0.953 (<0.5*, 4.54)
30	58.1 (41.0, 81.7)	34.0 (20.2, 52.5)	20.2 (8.69, 35.8)	11.9 (3.66, 25.0)	7.07 (1.59, 18.0)	2.69 (<0.5*, 9.78)	1.14 (<0.5*, 5.44)
40	77.5 (54.7, 109)	45.3 (27.0, 70.0)	26.9 (11.6, 47.7)	15.8 (4.88, 33.3)	9.43 (2.11, 24.0)	3.58 (<0.5*, 13.0)	1.53 (<0.5*, 7.26)
50	96.8 (68.3, 136)	56.6 (33.7, 87.5)	33.6 (14.5, 59.6)	19.8 (6.10, 41.7)	11.8 (2.64, 30.0)	4.48 (0.615, 16.3)	1.91 (<0.5*, 9.07)
65	126 (88.9, 177)	73.6 (43.8, 114)	43.7 (18.8, 77.5)	25.7 (7.94, 54.2)	15.3 (3.44, 38.9)	5.82 (0.800, 21.2)	2.48 (<0.5*, 11.8)

[1] See *Dosage and Administration (2)*
[2] End of Infusion
* Below the level of quantitation of 0.5 IU/dL

Table 4: Predicted Steady State Troughs [IU/dL] of FVIII Activity with 50 IU/kg of ELOCTATE Administered Every 3, 4, or 5 Days

Dosing Frequency		
Every 3 Days	**Every 4 Days**	**Every 5 Days**
Median (5th, 95% Prediction Interval)		
5.27 (0.774, 20.4)	2.32 (<0.5[1], 11.4)	1.10 (<0.5[1], 6.17)

[1] Below the level of quantitation of 0.5 IU/dL

A dosing regimen of 50 IU/kg every 5 days is predicted to yield troughs above 1 IU/dL in 53.4% of individuals and a dosing regimen of 65 IU/kg administered weekly is predicted to yield troughs above 1 IU/dL in 26.7% of the individuals treated.

CLINICAL PHARMACOLOGY RECOMMENDATION

- The results of the PK analyses and conclusions are acceptable.
- For prophylactic treatment rFVIIIFc dosing regimens of 50 IU/kg or 65 IU/kg every 5 days given to adults and children older than 6 years appear to be adequate to achieve and sustain therapeutic concentrations.
- For pediatric patients between 2 and 6 years of age the following "per kg bodyweight" dose adjustments are recommended:

  For prophylaxis, doses of up to 80 IU/kg every 3 days may be required. Alternatively, lower doses of 50 IU/kg every 2 days can be utilized**.**

  To control bleeding, repeat dosing every 12-24 hours if required for minor and moderate bleeding. For major bleeding, repeat dosing may be administered every 8-24 hours.

  For minor surgery, a single infusion may be sufficient. A repeat dose may be administered after 12-24 hours. For major surgery, careful monitoring of FVIII activity is required. Following an initial loading dose, repeat dosing may be administered after 6-24 hours.

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1. Study Title: A Phase 1/2a, open-label, crossover, dose-escalation, and multi-center study to determine the safety, tolerability, and pharmacokinetics of a single intravenous injection of rFVIIIFc in previously treated patients with severe hemophilia A (Study No. 997HA301).

Objectives:

Primary Objective:

To assess the safety and tolerability of single administration of two doses of rFVIIIFc (25 and 65 IU/kg) in previously treated patients (PTPs) aged 12 and above with severe hemophilia A.

Secondary Objectives:

- To determine the pharmacokinetic (PK) parameters after single administration of 25 and 65 IU/kg rFVIIIFc compared to Advate®.
- To determine the pharmacodynamic (PD) activity of FVIII over time for both doses of rFVIIIFc compared to Advate®.

Study Design

This was a Phase 1/2a open-label, crossover, dose-escalation, multi-center, and first-in-human study designed to evaluate the safety, tolerability, and pharmacokinetics of a single dose of rFVIIIFc (-b(4)---- formulation) given as an IV infusion over approximately 10 minutes in previously treated male patients (≥ 12 yr), diagnosed with severe hemophilia A (defined as <1% endogenous factor VIII). Advate® was chosen as the comparator because it is the current standard of care for hemophilia A.

A total of 16 previously treated patients (PTPs) were to be enrolled at 4 U.S. Centers and dosed with rFVIIIFc at 25 IU/kg (Cohort A: N = 6) or 65 IU/kg (Cohort B: N = 10). One week after the last subject received the 25 IU/kg rFVIIIFc dose, 10 new subjects were to be recruited for the 65 IU/kg cohort. Each subject in this cohort was to receive a single 65 IU/kg dose of Advate® followed by a 4-day (96 hour) PK profile, and then crossover to receive a single, open-label dose of rFVIIIFc for a 10-day (240 hour) PK profile. All subjects were to be followed for a 14-day and 28-day safety evaluation after administration of rFVIIIFc at either dose.

Blood samples were collected for FVIII activity PK evaluations:

1) for rFVIIIFc at predose, at 10 and 30 minutes, and at 1, 3, 6, 9, 24, 48, 72, 96, 120, and 168 hours post-injection for subjects administered either 25 IU/kg or 65 IU/kg of rFVIIIFc, and additionally at 192, 216, and 240 hours post-injection for those subjects administered with 65 IU/kg of rFVIIIFc).

2) for Advate® at predose, at 10 minutes, 30 minutes and 1, 3, 6, 9, 24, 48, and 72 hours post-injection for subjects administered either 25 IU/kg or 65 IU/kg of Advate® and additionally at 96 hours postinjection for subjects administered 65 IU/kg of Advate®.

Methods of Analysis

Blood samples were analyzed at central laboratories for rFVIIIFc and Advate®

- FVIII activity by a one-stage clotting assay (aPTT)
- FVIII activity by chromogenic substrate assay.

All patients enrolled in the study and who received any amount of rFVIIIFc were included in the evaluation for immunogenicity (antibody development).

PK parameters were calculated using an open 1-compartment model (software –b(4)----------). The primary PK analysis was based on one-stage (aPTT) clotting activity data.

Results:

a. FVIIIFc Activity Pharmacokinetics (one-stage clotting assay)

PK results are presented in Table 1a. The decline of FIX activity exhibited monoexponential disposition following an intravenous infusion over 10 minutes. The exposure parameters Cmax and AUCinf appear to be dose independent between 25 and 65 IU/kg.

Table 1a: rFVIIIFc activity PK parameters (arithmetic mean, 95-% CI) in hemophilia A patients (one-stage clotting assay)

PK-Parameter	**IV-Dose (IU/kg)**	
	25 (N=6)	65 (N=9)
Cmax (IU/dL)	60.9 [53, 69]	120 [104, 137]
AUCinf (h·IU/dL)	1510 [1150, 1870]	3060 [2060, 4050]
T½ (h)	19.2 [15, 24]	19.8 [15, 25]
CL (mL/kg/h)	1.72 [1.3, 2.2]	2.55 [1.6, 3.5]
V (mL/kg)	45.8 [39, 53]	63.6 [55, 72]
MRT (h)	27.6 [21, 34]	28.4 [21, 36]
IVR (IU/dL per IU/kg)	2.46 [2.1, 2.8]	1.85 [1.6, 2.1]
Time 1% (d)	4.5 [3.5, 5.5]	5.5 [4.0, 6.9]

Cmax = maximum observed activity, occurring at Tmax (baseline and residual drug subtracted); AUCinf = total AUC from time zero to infinity (Dose/CL); T½ = half-life; CL = clearance; IVR = incremental in-vivo recovery; MRT = mean residence time; V = volume of distribution; Time 1% = time after dose when FVIII activity has declined to 1 IU/dL above baseline

All time-related parameters of rFVIIIFc were approximately 50% higher than the corresponding Advate® parameters. The IR-value and V for both rFVIIIFc and Advate® were similar.

b. FVIIIFc activity pharmacokinetics (-b(4)---- cromogenic assay)

rFVIIIFc plasma concentrations declined in a monoexponential fashion following the short IV infusion. In general, the PK parameters estimated from the chromogenic activity assay were consistent with those from the one-stage (aPTT) clotting assay, with the exception of Cmax and AUCinf where the chromogenic assay yielded a higher estimation for both rFVIIIFc and Advate®.

Table 1b: rFVIIIFc activity PK parameters (arithmetic mean, 95-% CI) in hemophilia A patients (--b(4)----- chromogenic assay)

PK-Parameter	**IV-Dose (IU/kg)**	
	25 (N=6)	65 (N=9)
Cmax (IU/dL)	77.2 [66, 89]	190 [140, 239]
AUCinf (h·IU/dL)	1700 [1260, 2140]	4670 [3280, 6070]
T½ (h)	16.9 [14, 20]	21.2 [16, 27]
CL (mL/kg/h)	1.53 [1.2, 1.9]	1.7 [1.0, 2.4]
V (mL/kg)	36.3 [30, 43]	44 [38, 50]
MRT (h)	24.3 [20, 29]	30.5 [23, 39]
IVR (IU/dL per IU/kg)	3.12 [2.6, 3.6]	2.92 [2.2, 3.7]
Time 1% (d)	4.2 [3.4, 5.1]	6.3 [4.6, 8.0]

Cmax = maximum observed activity, occurring at Tmax (baseline and residual drug subtracted); AUCinf = total AUC from time zero to infinity (Dose/CL); T½ = half-life; CL = clearance; IVR = incremental in-vivo recovery; MRT = mean residence time; V = volume of distribution; Time 1% = time after dose when FVIII activity has declined to 1 IU/dL above baseline

The increased duration of activity of rFVIIIFc relative to Advate® was also demonstrated by FVIII activity measured by the chromogenic assay. Comparable Cmax, IR, and Volume values were observed between Advate® and rFVIIIFc at equivalent doses

Pharmacokinetic Conclusions

- Apparent dose-proportional increases in Cmax and AUCinf were observed for both rFVIIIFc assays following the administration of 25 and 65 IU/kg.
- The volumes and CL estimates were approximately similar across all doses.

Reviewer's Comment:

- The results of the PK analysis and applicant's conclusions are acceptable from a Clinical Pharmacology perspective.

2. Study Title: An open-label, multi-center evaluation of the safety, pharmacokinetics, and efficacy of recombinant, factor VIII Fc fusion protein (rFVIIIFc) in the prevention and treatment of bleeding in previously treated subjects with severe hemophilia A. (Study Number: 998HB102)

Study Design

This was a Phase 3, open-label, multinational, multicenter study to evaluate the safety, PK, and efficacy of rFVIIIFc (lyophilized powder) administered as an IV injection to subjects with severe hemophilia A (defined as < 1 IU/dL [<1%] endogenous FVIII activity) and ≥ 12 years of age, who had at least 150 prior exposure days to a concentrate or recombinant FVIII product. A total of 165 subjects were enrolled into 1 of 3 regimens and received study treatment according to the assigned treatment group:

Arm 1, Weekly Prophylaxis

Approximately 104 subjects received initially twice weekly dosing with 25 IU/kg of rFVIIIFc on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days to maintain a trough level of 1% to 3% (or higher, as clinically indicated).

- *Sequential PK Subgroup*

  On Day 0, 28 subjects received a single dose of Advate® 50 IU/kg followed by PK sampling over 72 hours (3 days) taken at the following time points: pre-dose, and at 30 minutes, 1, 6, 24, 48, 72 hours post-dose. Subjects then received a single dose of rFVIIIFc 50 IU/kg followed by PK sampling over 120 hours taken at pre-dose and 10/30 minutes, 1, 6, 24, 72, 96 and 120 hours post-dose.

  A second, repeat PK profiling occurred between week 12 and week 24 with a single dose of 50 IU/kg of rFVIIIFc. PK samples were obtained over 120 hours following the repeat dose using the same sampling schedule as for Day 0 rFVIIIFc dosing.

- *Non-Sequential PK Subgroup*

  Subjects in this subgroup received a single dose of rFVIIIFc 50 IU/kg on Day 0 (Baseline PK) followed by an abbreviated PK sampling over 96 hours: pre-dose, and at 10/30 minutes, 3, 72, and 96 hour post-dose.

  Once a subject completed the rFVIIIFc PK assessment, the initial dosing regimen and the subsequent determination of a tailored prophylaxis regimen were conducted in a manner similar to the procedure outlined for the Arm 1 PK Subgroup.

Arm 2, Weekly Prophylaxis

- Subjects received a single 65 IU/kg IV dose of rFVIIIFc on study Day 0 (Baseline PK) followed by abbreviated PK sampling up to 96 hours taken at pre-dose, and at 10/30 minutes, 3, 72, and 96 hour post-dose. Following the PK assessment and between scheduled visits, subjects treated bleeding episodes and all subjects were then administered a fixed dose of 65 IU/kg rFVIIIFc every 7 days. Approximately 20 subjects.

Arm 3, Episodic (On-demand) Regimen

- Subjects received a single 50 IU/kg IV dose of rFVIIIFc on Day 0 (Baseline PK) followed by abbreviated PK sampling up to 96 hours. The subjects in Arm 3 had PK samples drawn as follows: pre-dose, and at 10/30 minutes, 3, 72, and 96 hours after rFVIIIFc administration. Following the PK assessment and between scheduled visits, subjects treated bleeding episodes with rFVIIIFc doses between 10 and 50 IU/kg depending on the severity of the bleeding. Approximately 20 subjects.

In addition to the 3 treatment arms, there was a surgical subgroup and subjects from any arm were considered for enrollment in this subgroup.

Peak and trough measurements were carried out periodically, at nominal times spread over the whole course of study participation (such as at week 7, 14, 28, 38, 52, etc.). The surgical subgroup individuals were also sampled at various times during surgery and in the post-operative phase to ensure that the desired activity was maintained and to make necessary adjustments in the doses administered.

Assay Methodology and Analysis Software

The primary analysis of FVIII activity in plasma for Advate® and rFVIIIFc was done using by a validated one-stage clotting (aPTT) assay while a confirmatory analysis was done by a validated -b(4)------- chromogenic substrate assay. The lower limit of quantification (LLOQ) for the one-stage assay was 0.5 IU/dL.

Compartmental and confirmatory noncompartmental analyses were conducted for FVIII activity data using either –b(4)---------- software.

Pharmacokinetic Analyses

The estimated pharmacokinetic parameters for rFVIIIFc are summarized in Table 1. The maximum concentration (Cmax) was observed immediately following infusion. After administration of the 50 IU/kg dose, the mean increase in circulating FVIII activity from pre-infusion level was 2.26 IU/dL per IU/kg and the terminal elimination half-life (T½-β) was 19.7 hours. The PK profile of rFVIIIFc was stable over 14 weeks, with the time course of activity predictable from the first dose.

The PK evaluation of 11 adolescent subjects 12 to 17 years old showed that their PK profiles and the arithmetic means of PK parameters are similar to those of adults. Thus, the results indicate that for subjects 12 years of age or older, there is no requirement for age-based dose adjustment.

Compared with Advate®, rFVIIIFc showed a 1.53-fold increase in terminal T½.

Table 1: Estimated pharmacokinetic parameters (arithmetic mean, 95%-CI) in patients with severe hemophilia A. One-stage clotting assay (aPTT).

PK Parameters	**rFVIIIFc**
	50 IU/kg (N = 28)
Cmax (IU/dL)	109.0 (102, 116)
CL (mL/kg/h)	2.06 (1.8, 2.3)
V (mL/kg)	49.5 (47, 52)
T½ (h)	19.7 (17, 22)
MRT (h)	26.1 (23, 29
IVR (IU/dL per IU/kg)	2.26 (2.1, 2.4)
Time to 1% FIX activity (d)	5.1 (4.5, 5.7)

Cmax = observed maximum activity, CL = systemic clearance, V = volume of distribution, T½ = terminal elimination half-life, MRT = mean residence time, IVR = incremental in-vivo recovery, Time to 1% FIX activity = estimated time after dose when FIX activity has declined to approximately 1 IU/dL above baseline

Pharmacokinetic Conclusions

- The activity-time profiles for rFVIIIFc are adequately characterized by compartmental and noncompartmental analyses, and results from the one-stage assay were supported by those from the –b(4)----- chromogenic assay.
- The mean elimination half-life of rFVIIIFc was 19.7 hours after a dose of 50 IU/kg. Compared to Advate®, rFVIIIFc showed a 53% increase in terminal elimination half-life.
- Mean incremental recovery of rFVIIIFc was 2.26 IU/dL per 1 IU/kg.
- The PK profile of rFVIIIFc was stable over 14 weeks, with the time course of activity consistent with and predictable from the first dose.
- Plasma rFVIIIFc activity-time profiles by both assays were well-characterized and consistent across all treatment arms with relatively low inter-subject variability. The PK parameters were estimated with good precision.
- No subject had a confirmed positive inhibitor test result.
- There were 5 subjects with anti-rFVIIIFc binding antibody positive test results initially detected prior to the first dose of rFVIIIFc and 6 subjects with positive results first detected during treatment with rFVIIIFc. There was no evidence of a clinical impact of a positive anti-rFVIIIFc binding antibody test result.

Reviewer's Comments:

- The results of the PK analysis and subsequent conclusions are acceptable from a Clinical Pharmacology perspective.

3. Study Title: Population PK analysis of rFVIIIFc data. Study Number: CPP-12-026-BIIB031

Objectives:

- To develop a population pharmacokinetic model based on rFVIIIFc and Advate activity data which characterizes the pharmacokinetics of rFVIIIFc, in hemophilia A patients and to estimate the population parameters of this model.
- To implement the model(s) developed for simulation of prospective rFVIIIFc dosing regimens in support of the proposed label

Modeling Data Sets

The Advate modeling dataset included 16 individuals from the Phase 1/2A study (No. 998HA101) and 30 individuals from the Phase 3 study (No. 997HA301). A total of 688 records were included.

The rFVIIIFc modeling dataset included 16 individuals from the Phase 1/2A study (No. 998HA101) and 164 individuals from the Phase 3 study (No. 997HA301) yielding a net of 2050 observation records

Assay Methodology

For the purposes of this population PK analysis, activity data (baseline and residual corrected), measured by one-stage clotting assay (aPTT, LLOQ was 0.5 IU/dL), was used as a marker of rFVIIIFc pharmacokinetics (PK). Therefore, all references to PK in this report relate to activity.

PK Software

--b(4)---------- was used for population PK analysis (---b(4)----------)

Results and Discussion Summary:

The final population PK model for rFVIIIFc (*F82fin0F17*) was a two compartment model with covariates von Willebrand Factor (VWF) on CL, WT and Hematocrit (HCT) on V1.

The estimated parameters of the final model are shown in Table 1. The IIV of the activity was low to moderate. As a result of the inclusion of the VWF covariate on CL, the CV of the IIV on this parameter decreased by approximately 20%..

The base model for Advate (model *Adv0D*) is a two-compartment model with covariates weight on V1 and study on V2, IIV terms on CL, V1, and V2, common additive error and separate proportional residual error by study. The population PK parameters were estimated with very good precision and are close to the ones derived from the conventional –b(4)---- analysis.

As both the rFVIIIFc and the Advate models represent adequate descriptions of the observed activity – time data, they have been used for simulations of various dosing scenarios of interest. A

number of simulations were performed for dosing regimens that can be used in prophylaxis, for the treatment of bleeding episodes and in perioperative care.

Table 1: Final Model *F82fin0F17* population parameters and bootstrap-derived nonparametric 95% CI's

Parameter	Symbol	Population Estimate	Nonparametric 95% CI[a]
Clearance, CL, [dL/h]	$\Theta 1$	1.65	1.57 – 1.74
Exponent on VWF	$\Theta 10$	-0.343	-0.439 - -0.247
Central Volume, V1, [dL]	$\Theta 2$	37.5	36.5 – 38.4
Allometric exponent on V1	$\Theta 8$	0.382	0.271 – 0.499
Exponent on HCT	$\Theta 9$	-0.419	-0.656 – -0.208
Intercompartmental Clearance, Q, [dL/h]	$\Theta 3$	0.0746	0.0594 – 0.184
Peripheral Volume, V2, [dL]	$\Theta 4$	6.92	3.80 – 13.8
IIV on CL, [%]	$\eta 1$	24.3	20.5 – 27.7
IIV on V1, [%]	$\eta 2$	13.4	11.0 – 15.5
Correlation between IIV on CL and V1	$\eta 12$	0.548	N.C.[b]
IOV on CL, [%]	$\eta 3$	20.6	16.7 – 25.1
IOV on V1, [%]	$\eta 4$	12.0	7.46 – 16.3
Correlation between IOV on CL and V1	$\eta 34$	0.639	N.C.[c]
Additive error, Phase 1/2A study, [IU/dL]	$\Theta 5$	0.421	0.172 – 0.612
Additive error, Phase 3 study, [IU/dL]	$\Theta 6$	0.208	0.126 – 0.275
Proportional error, [%]	$\Theta 7$	13.6	12.0 – 15.3

[a] See file bootstrap results.csv, "percentile confidence intervals" in subdirectory Final/bootstrap/f820F17. Out of 1000 bootstraps, 14 runs with minimization terminated were skipped when calculating the bootstrap results.
[b] Nonparametric 95% CI of 0.00956 – 0.0264 for a population mean of the covariance ω_{12} of 0.0179
[c] Nonparametric 95% CI of 0.00579 – 0.0312 for a population mean of the covariance ω_{34} of 0.0158

Conclusions

The population PK analyses and simulations presented above provide a comprehensive quantitative characterization of the activity-time profiles for rFVIIIFc and Advate®. The conclusions from these analyses are summarized below:

- The population PK model for rFVIIIFc and Advate describes adequately the combined activity data from the Phase 1/2A and Phase 3 studies.
- The kinetics of rFVIIIFc activity displays a two-compartmental behavior. The major covariate for activity identified was von Willebrand Factor level on clearance.

- The results of the population PK analyses for rFVIIIFc and Advate® confirm that the clearance of rFVIIIFc is lower than the clearance of Advate®, while the volumes of distribution at steady state are very similar.

Reviewer's Comments:

- The results of the population PK analysis and simulations are not acceptable and the pharmacometric study report will not be used to guide new dosing regimens. Justification: based on the estimated population parameters of the final 2-compartment model the post-hoc calculated terminal half-life of rFVIIIFc is around 68 h. This is inconsistent with the estimated half-life determined in the Phase 1/2a study (≈ 19 h) and in the Phase 3 study (≈ 17 h). However, this analysis deficiency will not be considered for clinical pharmacology labeling of rFVIIIFc.
- Stochastic simulations (6000 virtual patients) to evaluate and support dosing regimens for routine prophylaxis were carried out by the reviewer covering 2 doses (50 IU/kg and 65 IU/kg) and were based on PK results of the Phase 1/2a study. Simulation results are presented in the following table and were sent to the Medical Reviewer. Based on these results, applicant's proposed dosing regimen of 65 IU/kg every 7 days is not acceptable, because nearly 75% of the patients will be under-dosed ($c_{trough,ss}$ < 1%). To achieve and sustain therapeutic concentrations in the majority of patients a dose of either 65 IU/kg or 50 IU/kg with a dosing frequency of every 5 days appears to be sufficient.

Dose [IU/kg]	**Dosing Frequency**	**C(trough,ss)** [IU/dL] Median [Perc: 5^{th}, 95^{th}]	**% Patients with C(trough,ss) > 1 IU/dL (1 %)**
65	q7d	0.73 [0.3, 1.5]	24 %
65	q6d	0.97 [0.4, 2.0]	48 %
65	q5d	1.66 [0.7, 3.4]	84 %
65	q4d	3.39 [1.5, 6.8]	99 %
50	q5d	1.40 [0.6, 2.8]	76 %
50	q4d	2.72 [1.2, 5.4]	98 %

ss = steady-state

4. Study Title (Study is ongoing):

An open-label, multicenter evaluation of safety, pharmacokinetics, and efficacy of recombinant coagulation factor VIII Fc fusion protein, in the prevention and treatment of bleeding episodes in pediatric subjects with hemophilia A. (Study Number: 8HA02PED)

Study Design

The pediatric study (8HA02PED) is an open-label, multicenter evaluation of the safety, PK, and efficacy of rFVIIIFc in pediatric PTPs with severe hemophilia A (defined as < 1 IU/dL [<1%] endogenous factor VIII [FVIII] as documented in medical records from a local clinical laboratory demonstrating < 1% FVIII coagulant activity or a documented genotype known to produce severe hemophilia A). Subjects are to be younger than 12 years of age at enrollment and have at least 50 exposure days (EDs) to recombinant or plasma-derived FVIII products prior to enrollment. The study recruitment target is for a minimum of 50 subjects (25 subjects < 6 years of age and 25 subjects 6 to <12 years of age) to complete approximately 26 weeks of treatment to obtain at least 50 EDs. The first subject was enrolled on 27 August 2012.

A washout period with no FVIII treatment is required prior to administration of prestudy FVIII and prior to rFVIIIFc. Eligible subjects undergo a PK evaluation of prestudy FVIII.

Once the PK results from the PK subgroup are available, the remaining subjects will proceed directly to twice-weekly prophylactic treatment following enrollment. A subject is allowed to undergo surgery in the study following a minimum of 5 EDs to rFVIIIFc with no safety concerns. After completing the PK assessments, subjects begin twice-weekly prophylactic treatment with rFVIIIFc with a starting regimen of 25 IU/kg on Day 1 and 50 IU/kg on Day 4. Subsequent adjustments to the dose can be made to maintain the subject's trough levels >1% or higher as clinically indicated.

For the aPTT and chromogenic assay, in the <6 years cohort, 15 subjects had a complete and evaluable prestudy FVIII PK profile and 10 subjects had a complete and evaluable rFVIIIFc PK profile. In the 6 to <12 years cohort, 25 subjects had a complete and evaluable prestudy FVIII PK profile and 24 subjects had a complete and evaluable rFVIIIFc PK profile.

At the Baseline Visit (28 days prior to Day 1) subjects received a single intravenous (IV) injection of prestudy FVIII (blood sample time points: pre-dose, 0, 0.5, 3, 24, and 48 h) and on Day 1 received a single IV injection of rFVIIIFc (blood sample time points: pre-dose, 0.5, 3, 24, 48, and 72 h). Both drugs were administered in the clinic under medical supervision at a nominal dose of 50 IU/kg given over 5 minutes.

Bioanalytical Methods and Data Analysis Software

Plasma FVIII activity was measured using a one-stage aPTT clotting assay and a –b(4)---chromogenic substrate assay, which were validated for rFVIIIFc, Advate®, and human FVIII in human plasma samples.

The FVIII activity-over-time profiles, corrected by residual drug, were analyzed by non-compartmental analysis (NCA) using –b(4)----------

Results (One Stage Clotting Assay)

FVIII activity increased immediately following IV injection of rFVIIIFc at 50 IU/kg in each age cohort. The relevant PK parameter estimates derived from noncompartmental analysis of aPTT activity data are compared to PK results from the Phase 3 study and shown in Table 1a.

Table 1a: Comparison of PK parameters of rFVIIIFc by age category: arithmetic mean (95% CI)

	Pediatric Study (8HA02PED)		Phase 3 Study (997HA301)	
	<6 Years (N = 10)	6 to <12 Years (N = 27)	12 to 17 Years (N = 11)	≥18 Years (N = 144)
IR (IU/dL per IU/kg)	1.887 (1.748, 2.025)	2.435 (2.021, 2.849)	1.846 (1.577, 2.116)	1.987 (1.893, 2.080)
DNAUC (IU*h/dL per IU/kg)	28.29 (22.12, 34.45)	43.70 (35.08, 52.31)	38.67 (34.29, 43.05)	46.12 (43.35, 48.89)
$t_{½}$ (h)	11.96 (9.55, 14.38)	14.59 (11.46, 17.71)	16.37 (14.12, 18.62)	17.84 (16.94, 18.73)
MRT (h)	16.37 (13.04, 19.71)	21.12 (16.76, 25.48)	23.13 (19.90, 26.36)	25.33 (24.09, 26.57)
CL (mL/h/kg)	3.881 (2.915, 4.847)	2.695 (2.299, 3.091)	2.658 (2.339, 2.976)	2.463 (2.310, 2.616)
V_{ss} (mL/kg)	58.7 (54.7, 62.6)	49.9 (44.4, 55.3)	60.3 (53.3, 67.3)	57.5 (55.4, 59.5)

For the purposes of this table, all treatment arms in the Phase 3 study have been grouped together.
CI = confidence interval; CL = clearance; DNAUC = dose-normalized area under the curve; IR= incremental recovery; MRT = mean residence time; PK = pharmacokinetic; rFVIIIFc = recombinant coagulation factor VIII Fc; $t_{½}$ = terminal half-life; V_{ss} = volume of distribution at steady state.

Some trends in the results were noted. Specifically, a decrease in the mean T½, mean residence time (MRT) and dose-normalized area under the curve (DNAUC) estimates, and an increase in the mean body-weight-normalized CL for pediatric subjects <12 years of age, compared to the adult (≥18 years of age) values, were evident (Table 1b, calculated by the Clinical Pharmacology reviewer). Trends in IR and Vss estimates were less pronounced.

In the Phase 3 study, rFVIIIFc showed a 1.51-fold increase in T½ (geometric mean ratio [95% confidence interval]: 1.51 [1.38, 1.64]) in comparison to the competitor Advate®. In the pediatric study, in which a variety of prestudy FVIII treatments were evaluated, the ratio of T½ for rFVIIIFc versus prestudy FVIII products ranged from 0.87 to 3.12 (1.22 to 2.11 in subjects receiving Advate® as prestudy FVIII).

Table 1b: Mean relative change (%) of relevant PK parameters grouped by age category (referenced to adult values = 100%)

PK Parameter	Pediatric Study (8HA02PED)		Phase 3 Study (997HA301)	
	2 to < 6 years (N=10)	6 to < 12 years (N=27)	12 – 17 years (N=11)	≥18 years (N=144)
T½ (h)	-33 %	-18 %	-8 %	100 %
CL (mL/h/kg)	+58 %	+9 %	+8 %	100 %

T½ = terminal half-life, CL = systemic clearance

Results (Two Stage Chromogenic Assay)

Similar to the aPTT assay, FVIII activity increased immediately following IV injection of rFVIIIFc at 50 IU/kg in each age cohort. PK parameters derived from the two-stage chromogenic assay data were generally consistent with those generated from the one-stage aPTT assay data.

Summary

Analyzing the pediatric FVIII PK data obtained to date together with the PK data obtained in adult and adolescent subjects, the following conclusions can be drawn:

- Compared to adults, there appears to be a substantial decrease in mean half-life T½ (-33%) and an increase in mean bodyweight adjusted systemic CL (+58%) in pediatric patients 2 to < 6 years of age. These differences should be taken into account when dosing children 2 to < 6 years of age. Specifically:

  ☐ For prophylaxis in children <6 years of age, doses of up to 80 IU/kg every 3-4 days may be required. Alternatively, lower doses of 25-50 IU/kg every 2 days can be utilized.

  ☐ To control bleeding, the increased clearance in the <6 year age group translates into a recommendation for repeat dosing every 12-24 hours if required for minor and moderate bleeding. For major bleeding, repeat dosing may be administered every 8-24 hours.

  ☐ For minor surgery, as in adults, a single infusion may be sufficient. A repeat dose may be administered in pediatric patients <6 years of age after 12-24 hours. For major surgery, careful monitoring of FVIII activity is required. Following an initial loading dose, repeat dosing may be administered after 6-24 hours.
- Consistent across age groups, rFVIIIFc is observed to have a prolonged T½ and reduced CL compared with other FVIII products.
- PK parameters derived from the –b(4)----- chromogenic assay data were generally consistent with those generated from the one-stage aPTT assay data.

Reviewer's Comments:

- In general, the results of the interim pediatric PK analysis and conclusions are acceptable from a Clinical Pharmacology perspective.

- To support clinical decisions for optimizing dosing regimens for routine prophylaxis, stochastic simulations (5000 virtual patients) were carried out by the reviewer covering 1 dose of 80 IU/kg given every 5, 4, or 3 days. The simulations were based on submitted preliminary PK results of the ongoing pediatric Phase 3 study. Results are shown in the following Table and were sent to the Medical Reviewer. In summary, to achieve and sustain therapeutic concentrations in the majority of pediatric patients a dose of 80 IU/kg with a dosing frequency of every 3 days appears to be sufficient.

Dose [IU/kg]	**Dosing Frequency**	**C(trough,ss)** [IU/dL] Median [Perc: 5^{th}, 95^{th}]	**% Patients with C(trough,ss) > 1 IU/dL (1 %)**
80	q5d	0.9 [0.5, 2.6]	40 %
80	q4d	1.2 [0.6, 5.2]	65 %
80	q3d	2.3 [0.8, 12.3]	90 %

Perc = percentile, ss = steady-state

- A final assessment, however, can only be made after submission of the final study report